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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/818,875	03/27/2001	Eric B. Kmiec	Napro-4	2466

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EXAMINER	
ANGELL, JON E	

ART UNIT	PAPER NUMBER
1635	26

DATE MAILED: 12/02/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/818,875	KMIEC ET AL.	
	Examiner	Art Unit	
	J. Eric Angell	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 September 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *25-38,40-54 and 56-78* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *75-78* is/are allowed.

6)☒ Claim(s) *25-38,40-54 and 56-69* is/are rejected.

7)☒ Claim(s) *70-74* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *07 August 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This Action is in response to the communication filed on 9/23/03. The amendment has been entered. Claims 25, 35-37, 40, 47, 57, 58 and 75 have been amended. Claim 55 has been cancelled. New claim 78 has been added. Claims 25-38, 40-54 and 56-78 are currently pending in the application and are examined herein.

2. Applicant's arguments are addressed on a per section basis. The text of those sections of Title 35, U.S. Code not included in this Action can be found in a prior Office Action. Any rejections not reiterated in this action have been withdrawn as being obviated by the amendment of the claims and/or applicant's arguments.

Specification

The objection to the specification has been withdrawn in view of the amendment which included the removal of the embedded hyperlinks.

Claim Objections

The objection to claim 50 has been withdrawn in view of Applicants persuasive arguments. The objection to claim 55 has been obviated by the cancellation of the claim.

Claim Rejections - 35 USC § 112, second paragraph

The rejection of claims under 35 USC 112, second paragraph have been obviated by the amendment. Therefore, the rejection of claims under 35 USC 112, second paragraph have been withdrawn.

Claim Rejections - 35 USC § 112, first paragraph (scope of enablement)

The rejection of claims under 35 USC 112, first paragraph (scope of enablement) have been withdrawn in view of the amendment which limits the claimed methods to cells in culture, cells in vitro, or cell free extracts. Additionally, Applicants arguments are persuasive with respect to the second scope of enablement rejection, wherein the claims were rejected for not being enabled for stem cell therapy. Therefore, the rejection of claims is withdrawn.

Claim Rejections - 35 USC § 103

1. The rejection of claims 25-38, 40-58 and 63-69 under 35 U.S.C. 103(a) as being obvious over Yamamoto et al. (Genetics 131:811-819; 1992, cited in IDS) in view of Meyer et al. (US Patent 6,136,601) has been withdrawn in view of the Applicants arguments.

Response to Arguments

1. Applicant's arguments, see pages 19-23 of the response filed 9/23/03, with respect to the rejection(s)of the instant claim(s) under 35 USC 103 have been fully considered and are

persuasive. Therefore, the rejection has been withdrawn. Specifically, Applicants argue that Meyer teaches that absolute requirement for a chemically reactive electrophilic crosslinking moiety to effect oligonucleotide-mediated sequence alteration, which is not present in Yamamoto's unmodified oligonucleotide (see arguments on p. 22 of the response). It is acknowledged that Meyer teaches the absolute requirement that the modified oligonucleotide comprises a chemically reactive electrophilic crosslinking moiety to effect oligonucleotide-mediated sequence alteration, and Yamamoto does not teach an oligonucleotide comprising such a moiety. Therefore, the rejection previously set forth has been withdrawn.

2. However, upon further consideration, a new ground(s) of rejection is made as set forth below.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 25-38, 40-58 and 63-69 are rejected under 35 U.S.C. 103(a) as being obvious over Yamamoto et al. (Genetics 131:811-819; 1992, cited in IDS) in view of Meyer et al. (US Patent 6,136,601).

The applied reference (Meyer) has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). For applications filed on or after November 29, 1999, this rejection might also be overcome by showing that the subject matter of the reference and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person. See MPEP § 706.02(l)(1) and § 706.02(l)(2).

It is noted that the new grounds of rejection were not necessitated by amendment, thus the instant action is made non-final.

Yamamoto teaches a method for targeted sequence alteration of a nucleic acid sequence using a single stranded oligonucleotide that does not form hairpin structures and which is fully complementary to the target sequence except one or more mismatches that are centrally located in the oligonucleotide. Specifically, Yamamoto teaches that the single stranded oligonucleotide is in the range of 17-121 nucleotides long which do not appear and are not disclosed as capable of forming a hairpin (e.g., see p. 813 Table 1; p. 814, Table 2, etc.). The oligonucleotide comprises a domain of at least 8 contiguous deoxyribonucleotides (e.g. all of the nucleotides of Yamamoto may be deoxyribonucleotides). Yamamoto teaches that the oligonucleotide can be used to make site-directed genetic alteration of double stranded DNA in S. cerevisiae (a yeast cell) (e.g., see p. 811, abstract).

Yamamoto does not teach that: 1) the oligonucleotide comprises base modifications, such as 2-O-Me or phosphorothioates; 2) the oligonucleotide can be used to make site directed sequence modification in other cell types such as bacteria or animal cells; and 3) that the oligonucleotide comprises a chemically reactive electrophilic crosslinking moiety that effects oligonucleotide-mediated sequence alteration.

However, Meyer also teaches a method for targeted sequence alteration of a nucleic acid using a single stranded oligonucleotide comprising a chemically reactive electrophilic crosslinking moiety to effect oligonucleotide-mediated sequence alteration wherein the oligonucleotide does not form hairpin structures and which can be used to make targeted genetic alterations in nucleic acids present within cells. Meyer teaches that the oligonucleotide can be comprised of modifications which decrease the oligonucleotides sensitivity to nuclease degradation, including 2-O-Me base analogs and phosphorothioate linkages (e.g., see col. 7, lines

29-60). An oligonucleotide comprising the 2-O-Me or phophorothioate modifications would necessarily comprise these modifications as terminal modifications (e.g., see col. 7, lines 29-67). Meyer also teaches that the oligonucleotides can be used to make targeted genetic alterations in bacteria cells as well as animal cells, including human cells (e.g., see col. 14, lines 28-31). Furthermore, Meyer indicates that the oligonucleotide could be used to make genetic alterations in double stranded DNA that is present in chromosomes in cells such as plant, fungus, bacteria, etc.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time of filing to modify the oligonucleotide used by Yamamoto such that it comprised a chemically reactive electrophilic crosslinking moiety to effect oligonucleotide-mediated sequence alteration, as well as the base modifications 2-O-Me or phosphorothioates taught by Meyer, with a reasonable expectation of success.

One of ordinary skill in the art would have been motivated to make the alterations to the Yamamoto oligonucleotide because Meyer teaches that it is "desirable to ensure that the majority of modified oligonucleotides that bind to a target sequence become covalently attached to that sequence...Consequently, the mutagenic efficiency of the method of the present invention is much higher than that of previous methods..." (See column 16, lines 16-38). Thus indicating that oligonucleotides intended to be used for site directed mutagenesis should comprise a chemically reactive electrophilic crosslinking moiety to effect oligonucleotide-mediated sequence alteration in order to increase efficiency. Additionally, Meyer teaches that 2-O-Me and phosphorothioate modifications are preferable modifications to have in oligonucleotides used for site directed alterations in cells.

Furthermore, it would have been prima facie obvious that the oligonucleotide could have been used to target any double stranded nucleic acid sequence such as artificial chromosomes, episomal genomic DNA, or nucleic acids present in other mammalian cells such as rodent or monkey cells, as all of these potential target sequences would have been well known to one of skill of in the art based on the disclosure in the present specification.

Claim Rejections - 35 USC § 103

6. Claims 25-30, 37, 38, 40, 44-47 and 53-62 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Yamamoto et al. (Genetics 131:811-819; 1992, cited in IDS) in view of Wengel et al. (WO 99/14226, cited in IDS) for the reasons of record.

Response to Arguments

7. Applicant's arguments filed 9/23/03 have been fully considered but they are not persuasive.

8. Applicants argue that the instant specification indicates that although different modifications are known to have different effects on the nuclease resistance of oligonucleotides or the stability of duplexes formed by such oligonucleotides, they have found that it is not possible to predict "which of any particular known modification **would be most useful** for any given alteration event" (See p. 24 of the response, referring to p. 5, lines 13-20 of the specification; emphasis added by Examiner). Therefore, Applicants argue that one of skill in the art would not have been motivated to make such alterations, nor would said artisan have any expectation of success. Applicants also argue that Wengel does not speak to the effects of LNA

modifications "on targeted sequence alteration reactions performed in the presence of, **and mediated by, cellular repair proteins as claimed by applicants.**" (See p. 24-25 of the response; emphasis added).

9. In response, it is respectfully pointed out that although one of skill in the art might not be able to predict which particular modification **would be most useful,** this would not effect the artisan's motivation or expectation of success. That is, it is irrelevant that the artisan could not predict the most useful modification, the fact that the modification(s) would have any effect would be sufficient motivation, and would provide an expectation of success. Furthermore, there is no evidence presented indicating unexpected results. With respect to the argument that Wengel does not speak to the effects of LNA modifications "on targeted sequence alteration reactions performed in the presence of, and mediated by, cellular repair proteins as claimed by applicants." It is respectfully pointed out that the claims do not indicate that the cellular repair proteins mediate the targeted alteration reactions. Furthermore, Yamamoto does teach that the oligonucleotide is used for targeted sequence alterations in cells, which would necessarily be in the presence of repair proteins. Therefore, it appears that Applicants are arguing the references individually. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

10. Claims 25-30, 37, 38, 40, 44-47, 53-58 and 63-69 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Yamamoto et al. (Genetics 131:811-819; 1992, cited in IDS) in view of Barracchini for the reasons of record.

Response to Arguments

11. Applicant's arguments filed 9/23/03 have been fully considered but they are not persuasive.

12. Applicants argue that for the reasons indicated in the response to the 103 rejection based on Yamamoto in view of Wengel, the effect of such modifications on targeted sequence alteration in the presence of cellular repair proteins was not and could not have been predicted, nor could any such modification have been attended a reasonable expectation of success (see arguments on p. 26-27 or response).

13. In response, as indicated above although one of skill in the art might not be able to predict which particular modification **would be most useful**, this would not effect the artisan's motivation or expectation of success. That is, it is irrelevant that the artisan could not predict the most useful modification, the fact that the modification(s) would have any effect would be sufficient motivation, and would provide an expectation of success. With respect to the argument that the Barrachchini reference does not speak to the effects of modifications on targeted sequence alteration reactions performed in the presence of, and mediated by, cellular repair proteins as claimed by applicants. It is respectfully pointed out that the claims do not indicate that the cellular repair proteins mediate the targeted alteration reactions. Furthermore, Yamamoto does teach that the oligonucleotide is used for targeted sequence alterations in cells, which would necessarily be in the presence of repair proteins. Therefore, it appears that

Applicants are arguing the references individually. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Allowable Subject Matter

14. Claims 75-78 are allowed.

15. Additionally, it is noted that amending claim 25 to indicate that the oligonucleotide "consists essentially of" the limitations described in claim 25 would obviate the rejection under 35 USC 103 based on Yamamoto in view of Meyer.

Claim Objections

16. Claims 70-74 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Eric Angell whose telephone number is (703) 605-1165. The examiner can normally be reached on M-F (8:00-4:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (703) 308-0447. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

J. Eric Angell, Ph.D.
AU 1635

DAVE T. NGUYEN
PRIMARY EXAMINER